



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

09/914,451

12/20/2001

Jesper Z. Haeggstrom

PVZ-006USRCE

4167

959 7590 03/04/2009

LAHIVE & COCKFIELD, LLP  
FLOOR 30, SUITE 3000  
ONE POST OFFICE SQUARE  
BOSTON, MA 02109

EXAMINER

KIM, ALEXANDER D

ART UNIT

PAPER NUMBER

1656

MAIL DATE

DELIVERY MODE

03/04/2009

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Advisory Action</b> <b>Before the Filing of an Appeal Brief</b>	<b>Application No.</b> 09/914,451	<b>Applicant(s)</b> HAEGGSTROM ET AL.	
	<b>Examiner</b> ALEXANDER D. KIM	<b>Art Unit</b> 1656	

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 16 January 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☐ The period for reply expires \_\_\_\_\_ months from the mailing date of the final rejection.  
 b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

#### AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
 (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);  
 (b) ☐ They raise the issue of new matter (see NOTE below);  
 (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
 (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
 5. ☒ Applicant's reply has overcome the following rejection(s): 112, first.  
 6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
 7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
 The status of the claim(s) is (or will be) as follows:  
 Claim(s) allowed: \_\_\_\_\_.  
 Claim(s) objected to: 60,61,68,70,72,76,78 and 79.  
 Claim(s) rejected: \_\_\_\_\_.  
 Claim(s) withdrawn from consideration: \_\_\_\_\_.

#### AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
 9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
 10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

#### REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:  
See Continuation Sheet.  
 12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_  
 13. ☐ Other: \_\_\_\_\_.

/JON P WEBER/  
 Supervisory Patent Examiner, Art Unit 1656/7

Continuation of 11. does NOT place the application in condition for allowance because: Applicant's amendment after final rejection, filed on 01/16/2009, is acknowledged and has been entered. The previous rejections under 35 USC 112, first paragraph, are withdrawn by virtue of Applicants' amendment. The request for reconsideration in the reply filed on 01/16/2009 has been considered, however, the amendment does not place the application in condition for allowance. Claim 60, 61, 68, 70, 72, 76, 78 and 79 would be objected because the claimed method is drawn to a method having step of co-crystallizing in the presence of an inhibitor bestatin; wherein the bestatin is bound to the active site of the LTA4 hydrolase active site. Thus, reciting "co-crystallizing" is more appropriate and clear compared to reciting "crystallizing".

Applicants proposed amendments filed after a Final rejection on 01/16/2009 are acknowledged and have been considered. The amendments have been entered, however, said amendments do not place the application in condition for allowance for minor informalities. The request for reconsideration has also been considered and in attempt to facilitate the instant application to allowance, the Examiner proposed some modifications to the instant claims which would place said application in condition for allowance (see attachment below). However, Applicants were unable to reach a decision upon the Examiner's proposed amendments within the amount of time available. Thus, while the instant claim amendments have been entered, as noted, the claims are not in condition for allowance.

60. A method of identifying compounds that bind to a leukotriene A4 (LTA4) hydrolase comprising the amino acid sequence of SEQ ID NO: 1, the method comprising the steps of:

(a) co-crystallizing a purified LTA4 hydrolase to form an LTA4 hydrolase co-crystal, wherein crystallization is performed as liquid liquid diffusion in a capillary using equal volumes of a buffer: enzyme solution consisting of comprising:

i) a buffer solution consisting of 28% PEG8000, 0.1 M Na-acetate, 0.1 M imidazole at a pH of 6.8 and with 5 mM YbC13 as an additive; and

ii) an enzyme solution consisting of 5 mg/ml LTA4 hydrolase comprising the amino acid sequence of SEQ ID NO:1 in 10 mM Tris-HCl at a pH of 8, supplemented with 1 mM bestatin;

wherein the crystallization results in a LTA4 hydrolase crystal having the space group P21212 and the unit cell dimensions  $a=67.59 \text{ \AA}$ ,  $b=133.51 \text{ \AA}$ , and  $c=83.40 \text{ \AA}$  and wherein  $\alpha=\beta=\gamma=90^\circ$ ;

(b) determining the atomic coordinates of said LTA4 hydrolase co-crystal; and

(c) screening the atomic coordinates of a set of candidate compounds against the atomic coordinates of said LTA4 hydrolase co-crystal obtained in step a) to identify compounds that bind to the LTA4 hydrolase;

61. The method of claim 60, wherein the LTA4 hydrolase is purified by adsorption chromatography on hydroxyapatite and anion-exchange chromatography.

62-67. Cancelled.

68. The method of claim 60, wherein the atomic coordinates of said LTA4 hydrolase co-crystal correspond to the atomic coordinates defining atom 1 to atom 4876 as set forth in Table 9.

69. Cancelled.

70. A method of identifying an inhibitor of LTA4 hydrolase comprising the amino acid sequence of SEQ ID NO:1, the method comprising the steps of:

(a) co-crystallizing a purified LTA4 hydrolase to form a co-crystal and thereafter determining its three-dimensional structure, wherein crystallization is performed as liquid liquid diffusion in a capillary using equal volumes of a buffer: enzyme solution consisting of:

i) a buffer solution consisting of 28% PEG8000, 0.1 M Na- acetate, 0.1 M imidazole at a pH of 6.8 and with 5 mM YbC13 as an additive;

ii) an enzyme solution consisting of 5 mg/ml LTA4 hydrolase comprising the amino acid sequence of SEQ ID NO:1 in 10 mM Tris-HCl at a pH of 8, supplemented with 1 mM bestatin; wherein the crystallization results in a LTA4 hydrolase crystal having the space group P21212 and the unit cell dimensions  $a=67.59 \text{ \AA}$ ,  $b=133.51 \text{ \AA}$ , and  $c=83.40 \text{ \AA}$  and wherein  $\alpha=\beta=\gamma=90^\circ$ ; and

iii) determining the atomic coordinate of the co-crystal;

(b) identifying at least one potential inhibitor that is at least in part complementary to the LTA4 hydrolase by the use of the atomic coordinate structure of the co-crystal complex obtained in step a);

(c) soaking a co-crystallized LTA4 hydrolase as obtained in step a) with a solution of a potential inhibitor identified in step b) to obtain a complex of the crystal of said LTA4 hydrolase and said potential inhibitor; and

(d) performing X-ray crystallography of the crystal complex of LTA4 hydrolase and said potential inhibitor to determine the structure thereof, thereby identifying the potential inhibitor as an inhibitor of LTA4 hydrolase.

71. The method of claim 70, wherein the LTA4 hydrolase is purified by adsorption chromatography on hydroxyapatite and anion-exchange chromatography.

72. Cancelled.

73-75. Cancelled.

76. The method of claim 70, wherein the atomic coordinates of said LTA4 hydrolase crystal correspond to the atomic coordinates defining atom 1 to atom 4876 as set forth in Table 9.

77. Cancelled.

78. The method of claim 70, further comprising the step of refining the structure of said potential inhibitor obtained in step d) via computer modeling using data obtained from the X-ray crystallography in step d) and repeating steps b)-d).

79. Cancelled.

80-86. Cancelled.